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09/444,335	11/19/1999	GRIGORI N. ENIKOLOPOV	CSHL99-05	8515

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[REDACTED] EXAMINER

SCHNIZER, RICHARD A

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1635

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38

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)
	09/444,335	ENIKOLOPOV ET AL.
	Examiner Richard Schnizer	Art Unit 1635

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) Responsive to communication(s) filed on 23 July 2002.

2a) This action is FINAL. 2b) This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4) Claim(s) 1-79 is/are pending in the application.

4a) Of the above claim(s) 25-50 is/are withdrawn from consideration.

5) Claim(s) _____ is/are allowed.

6) Claim(s) 1-24 and 51-79 is/are rejected.

7) Claim(s) _____ is/are objected to.

8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) The proposed drawing correction filed on _____ is: a) approved b) disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.

12) The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) All b) Some * c) None of:

1. Certified copies of the priority documents have been received.
2. Certified copies of the priority documents have been received in Application No. _____.
3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) The translation of the foreign language provisional application has been received.

15) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) <input type="checkbox"/> Notice of References Cited (PTO-892)	4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____.
2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)	5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)
3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) <u>24</u> .	6) <input type="checkbox"/> Other: _____

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DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7/23/02 has been entered.

An amendment and an information disclosure statement were received and entered as Paper Nos. 23 and 24 on 7/23/02.

A supplemental amendment and the Declaration of Dr. Hoffman were received and entered as Paper No. 25 on 8/25/02.

Claims 1-79 are pending. Claims 25-50 were withdrawn from consideration in Paper No. 13, as being drawn to a non-elected invention. Claims 1-24 and 51-79 are under consideration in this Office Action.

Rejections Withdrawn

The rejection of claims 1-17, 19-24, and 51-79 under 35 U.S.C. 102 is withdrawn in view of Applicant's amendments.

Claim Rejections - 35 USC § 103

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The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-24, 51-71, 78, and 79 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zimmerman (1994) in view of Chiochetti (1997) for the reasons of record in Paper Nos. 13 and 17.

Claims 51-79 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zimmerman (1994) in view of Chiochetti (1997), Yeh et al (Proc. Nat. Acad. Sci. USA 92:7306-7040, 7/1995), Lois et al (Science 264(5162):1145-1148, 5/1994), and Reynolds et al (Science 255(5052):1707-1710, 3/1992) for the reasons of record in Paper No. 17.

Zimmerman who teaches a method of making a transgenic animal comprising a lac-Z transgene under control of the promoter and second intron enhancer of the rat nestin gene, and the detection of neuronal stem cells in these animals for the purpose of analyzing gene expression in these cells. See entire document, especially abstract; page 11, last sentence of paragraph bridging columns 1 and 2; sentence bridging pages 11 and 12; Table 1, pages 12 and 13, particularly constructs B, C, and F; Fig. 2 on page 15; and page 23, fourth full paragraph. Zimmerman does not teach a method of measuring multipotent stem and progenitor cells wherein the measurement step is carried out in a live animal.

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Chiochetti teaches that green fluorescent protein (GFP) is a more powerful and sensitive tool for studying gene expression in transgenic animals than is beta galactosidase. See entire document, especially page 202, column 1, lines 5-7. Chiochetti also teaches that GFP allows direct imaging in living cells, and suggests that changes in gene expression in living tissues could be examined. See page 201, column 1, lines 11-14.

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the method of Zimmerman by substituting green fluorescent protein for beta galactosidase, and to study gene expression in neuronal stem cells in living animals and their organs and tissues. One would have been motivated to do so because Chiochetti teaches that GFP allows direct imaging in living cells, and suggests that changes in gene expression in living tissues could be examined through the use of GFP. See page 201, column 1, lines 11-14. Furthermore, Yeh teaches that GFP can be monitored in intact, living embryos, and can be used for a variety of purposes including measurement of dynamic changes in gene expression in living tissue; lineage analysis; and monitoring cell migrations and changes in cell shape. See abstract; the last two sentences of the first full paragraph of column 2 on page 7036; page 7040, column 1, lines 5-9, and first two sentences of paragraph bridging columns 1 and 2 on page 7040. In addition, Lois et al teach the study of migration of neuronal precursors in adult mammalian brain, and Reynolds teaches that adult neuronal stem cells express nestin. See abstracts. Given the teachings of the prior art as discussed above, one of ordinary skill in the art would have been motivated to use a transgenic animal comprising a GFP sequence under the control of nestin

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regulatory sequences to follow neuronal precursor migration in living animals. In summary, the prior art provides explicit statements that GFP is superior to beta galactosidase for use in transgenic animals, and that it should be used to study cells of transgenic animals *in vivo*. The prior art also teaches that nestin transcription control sequences can be used to study neuronal precursor cells, and provides motivation to examine the transcriptional activities of these cells as well as their migration and morphology. Armed with this information, one of ordinary skill in the art would clearly be motivated to use nestin/GFP constructs in transgenic animals for the purpose of studying neuronal precursor populations.

Thus the invention as a whole was *prima facie* obvious.

Response to Arguments

Applicant's arguments, filed 7/23/02, and 8/6/02, and the Declaration of Dr. Hoffman, filed 8/6/02, have been fully considered but they are not persuasive.

At page 9 of the response, Applicant asserts that Zimmerman does not teach or suggest selection of the specific elements included in the claimed regulatory sequence of a mammalian nestin gene. This is incorrect. Applicant's attention is directed to Table 1, constructs B, C, and F which are transgenes comprising the nestin promoter and second intron enhancer. Applicant's arguments that expression was not affected by replacement of the nestin promoter with the TK promoter are superfluous. The claims require a transgene operably linked to a nestin promoter and at least a fragment of a nestin second intron. Zimmerman teaches this.

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At page 10 of the response Applicant asserts that Chiochetti does not remedy the deficiencies of Zimmerman because Chiochetti does not teach a transgenic animal comprising a nestin promoter and at least a fragment of a nestin second intron operably linked to a marker fluorescent protein. This is unpersuasive because Chiochetti need not teach all these elements. Zimmerman teaches a transgenic animal comprising a nestin promoter and at least a fragment of a nestin second intron operably linked a lac Z gene. Chiochetti teaches that green fluorescent protein is a more powerful and sensitive tool for studying gene expression in transgenic animals than is beta galactosidase. See entire document, especially page 202, column 1, lines 5-7.

Chiochetti also teaches that GFP allows direct imaging in living cells, and suggests that changes in gene expression in living tissues could be examined. See page 201, column 1, lines 11-14.

Applicant argues at page 10, paragraph 2 that the cited references do not expressly suggest the claimed invention. However, it is well established in case law that a reference must be considered not only for what it expressly teaches, but also for what it fairly suggests. In re Burkel, 201 USPQ 67 (CCPA 1979). Furthermore, in the determination of obviousness, the state of the art as well as the level of skill of those in the art are important factors to be considered. The teaching of the cited references must be viewed in light of these factors. It is noted, that the test for combining references is not what the individual references themselves suggest, but rather what the combination of disclosures taken as a whole would have suggested to one of ordinary skill in the art. In re McLaughlin, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). For the purpose of combining references, those references need not explicitly suggest combining teachings, much

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less specific references. In re Nilssen, 7 USPQ2d 1500 (Fed. Cir. 1988). Applicant has failed to show why one of ordinary skill in the art would have ignored the suggestion of Chiochetti to use GFP as a reporter gene, rather than lac Z, when making transgenic animals for the study of neural stem cells as suggested by Zimmerman.

At pages 10 and 11 of the response, Applicant discusses the unpredictability of the claimed invention. Applicant asserts one of ordinary skill in the art, when combining Chiochetti and Zimmerman, would expect to obtain the level of fluorescence intensity observed by Chiochetti, and that this level is less than that observed in the instant invention. In support of this argument, Applicant notes that Chiochetti identified transgenic animals by PCR, or by fluorescence analysis using specific excitation and detection wavelengths, rather than by fluorescence in response to a hand held UV lamp. This is unpersuasive because the fact that animals were identified by these means does not mean that they were not identifiable by hand held UV fluorescence. Applicant has failed to show that the animals of Chiochetti were not identifiable by this method. Applicant further argues that because Chiochetti used appropriate filters to reduce background noise when observing the GFP signal, that the signal to noise ratio of Chiochetti was less than that of Applicant. This argument is unpersuasive because it lacks support, particularly in view of the Declaration of Dr. Hoffman and Data Exhibit IE and IIA. Dr. Hoffman indicates that these images were generated using the techniques taught in Yang et al (2002a) (Exhibit B). Yang (2002a) teaches that images were generated using selective GFP excitation and a band pass filter. See page 3827, column 2, paragraph 3. Yet despite the increase

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in signal to noise ratio afforded by such methods, there appears to be substantial autofluorescence in the intestines and paws of the imaged mouse in Data Exhibit IE, and between the shoulders of the mouse imaged in Data Exhibit IIA. Even though Applicant argues, and Dr. Hoffman declares, in Paper No. 25 that the fluorescence intensity of the obtained mice is unexpectedly great, Applicant provides no direct evidence that the observed fluorescence intensity or signal to noise ratio is any greater than that produced by Chiochetti. For these reasons the rejection is maintained.

At page 12, paragraph 2, Applicant requested clarification of why claims 51-79 were rejected as obvious over Zimmerman, Chiochetti, Yeh, Lois, and Reynolds, when the rejection seemed to be address claims 72-77. By way of clarification, it is noted that if claims 72-77 are obvious, then claims 51-71, 78, and 79 must also be obvious because claims 72-77 require the compositions and methods of claims 51-71, 78, and 79. It is also noted that if claims 51-71, 78, and 79 are obvious over Zimmerman and Chiochetti alone, then these claims, in addition to claims 72-77, must also be obvious over the combination of Zimmerman, Chiochetti, Yeh, Lois, and Reynolds.

Applicant's arguments at page 13 of the response regarding this rejection are based on the assertion that claims 51-71, 78 and 79 are patentable over Zimmerman and Chiochetti. This argument is unpersuasive for the reasons discussed above. Applicant also argues at page 14 of the response that the claimed invention is not obvious because neither Zimmerman nor Chiochetti teach a method of assay performed on a live animal. This is unpersuasive because

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neither Zimmerman nor Chiochetti was relied upon for this teaching. Yeh was relied upon to teach that GFP can be monitored in intact, living embryos, and can be used for a variety of purposes including measurement of dynamic changes in gene expression in living tissue; lineage analysis; and monitoring cell migrations and changes in cell shape. See abstract; the last two sentences of the first full paragraph of column 2 on page 7036; page 7040, column 1, lines 5-9, and first two sentences of paragraph bridging columns 1 and 2 on page 7040. Lois et al teach the study of migration of neuronal precursors in adult mammalian brain, and Reynolds teaches that adult neuronal stem cells express nestin. See abstracts. Given the teachings of the prior art as discussed above, one of ordinary skill in the art would have been motivated to use a transgenic animal comprising a GFP sequence under the control of nestin regulatory sequences to follow neuronal precursor migration in living animals. Applicant is reminded that a reference must be considered not only for what it expressly teaches, but also for what it fairly suggests. In re Burkel, 201 USPQ 67 (CCPA 1979). Furthermore, in the determination of obviousness, the state of the art as well as the level of skill of those in the art are important factors to be considered. The teaching of the cited references must be viewed in light of these factors. It is noted, that the test for combining references is not what the individual references themselves suggest, but rather what the combination of disclosures taken as a whole would have suggested to one of ordinary skill in the art. In re McLaughlin, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

The rejection is maintained.

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Conclusion

No claim is allowed.

This application is request for continued examination of applicant's earlier Application No. 09/444,335. All claims are drawn to the same invention claimed in the earlier application and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the earlier application. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action in this case. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no, however, event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

This application contains claims **25-50** drawn to an invention nonelected with traverse in Paper No. 12. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

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Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 703-306-5441. The examiner can normally be reached Monday through Friday between the hours of 6:20 AM and 3:50 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John Leguyader, can be reached at 703-308-0447. The FAX numbers for art unit 1632 are 703-308-4242, and 703-305-3014. Additionally correspondence can be transmitted to the following RHTFAX numbers: 703-872-9306 for correspondence before final rejection, and 703-872-9307 for correspondence after final rejection.

Inquiries of a general nature or relating to the status of the application should be directed to the Patent Analyst Trina Turner whose telephone number is 703-305-3413.

Richard Schnizer, Ph.D.



JAMES KETTER
PRIMARY EXAMINER